Intraoperative Secondary Insults During Orthopedic Surgery in Traumatic Brain Injury

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Background: Secondary insults worsen outcomes after traumatic brain injury (TBI). However, data on intraoperative secondary insults are sparse. The primary aim of this study was to examine the prevalence of intraoperative secondary insults during orthopedic surgery after moderate-severe TBI. We also examined the impact of intraoperative secondary insults on postoperative head computed tomographic scan, intracranial pressure (ICP), and escalation of care within 24 hours of surgery.

Materials and Methods: We reviewed medical records of TBI patients 18 years and above with Glasgow Coma Scale score <13 who underwent single orthopedic surgery within 2 weeks of TBI. Secondary insults examined were: systemic hypotension (systolic blood pressure <90 mm Hg), intracranial hypertension (ICP >20 mm Hg), cerebral hypotension (cerebral perfusion pressure <50 mm Hg), hypercarbia (end-tidal $CO_2>40$ mm Hg), hypocarbia (end-tidal $CO_2<30$ mm Hg in absence of intracranial hypertension), hyperglycemia (glucose >200 mg/dL), hypoglycemia (glucose <60 mg/dL), and hyperthermia (temperature $>38^{\circ}$C).

Results: A total of 78 patients (41 [18 to 81] y, 68% male) met the inclusion criteria. The most common intraoperative secondary insults were systemic hypotension (60%), intracranial hypertension and cerebral hypotension (50% and 45%, respectively, in patients with ICP monitoring), hypercarbia (32%), and hypocarbia (29%). Intraoperative secondary insults were associated with worsening of head computed tomography, postoperative decrease of Glasgow Coma Scale score by ≥ 2, and escalation of care. After Bonferroni correction, association between cerebral hypotension and postoperative escalation of care remained significant ($P<0.001$).

Conclusions: Intraoperative secondary insults were common during orthopedic surgery in patients with TBI and were associated with postoperative escalation of care. Strategies to minimize intraoperative secondary insults are needed.

Key Words: traumatic brain injury, intraoperative, secondary insult, extracranial surgery, hypotension, anesthesia

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Traumatic brain injury (TBI) contributes to 30% of all injury-related deaths in the United Sates and each year approximately 1.7 million people suffer a TBI leading to 275,000 hospitalizations and 52,000 deaths.[1] The estimated direct and indirect medical cost of TBI management amounts to >$76.5 billion annually in the United States.[2] Secondary physiological insults such as hypotension, hypoxia, intracranial hypertension, hypercarbia, and hypocarbia are known to adversely impact outcomes after TBI.[3–8] Although previous studies have examined secondary insults in the prehospital period, during transportation to a tertiary care center, in the emergency department and in the intensive care setting,[3–8] data on intraoperative secondary insults are limited.[9,10] Moreover, patients with TBI frequently have associated orthopedic injuries requiring surgical intervention and data on secondary insults during orthopedic surgery in TBI and their impact on neurological outcomes are sparse and old.[11–14]

The importance of intraoperative and anesthetic period in TBI management is increasingly being recognized[15] and intraoperative data elements have recently been incorporated in the common data elements[16] for TBI recommended by the National Institute of Health (http://www.commondataelements.ninds.nih.gov/). Given the advances in anesthetic and intraoperative management in general, and the modification of clinical care guidelines for TBI management (such as change in the recommended cerebral perfusion pressure [CPP] goal to 50 to 70 mm Hg),[17] it is important to quantify the current burden of intraoperative secondary insults and examine their impact. We have previously reported on intraoperative secondary insults during craniotomy for TBI[9,10] but secondary insults in other surgical settings were not examined. The primary aim of this retrospective study

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was to examine the prevalence of intraoperative secondary insults during orthopedic surgery within 2 weeks of moderate-severe TBI. We also examined the effect of timing of orthopedic surgery on the secondary insults and the impact of intraoperative secondary insults on postoperative head computed tomographic (CT) scan, intracranial pressure (ICP), and escalation of care within 24 hours.

MATERIALS AND METHODS

Inclusion/Exclusion Criteria

After Institutional Review Board approval, we retrospectively reviewed the electronic medical and anesthesia records of TBI patients 18 years and above with admission Glasgow Coma Scale (GCS) score <13 who underwent single orthopedic surgery for long bone or pelvic injuries within 2 weeks of TBI at Harborview Medical Center (level-1 trauma center) between 2007 and 2011. Patients below 18 years of age, those with admission GCS score ≥ 13, those who had associated chest/lung/spinal injuries those who underwent >1 extracranial surgery, or surgery beyond 2 weeks of TBI were excluded. The requirement for written informed consent was waived by the IRB.

Data Sources

The list of eligible patients was generated using the institutional trauma registry matched against the electronic anesthesiology database. The trauma registry was queried to generate a list of patients admitted during the study period with all of the following criteria: (1) ICD-9 (International Classification of Diseases, ninth revision) codes reflecting diagnoses of TBI-related cerebral concussion, contusion, subarachnoid/subdural/extradural hemorrhage, and unspecified injury; (2) age 18 years and above; (3) admission GCS score <13; and (4) associated orthopedic injuries. This list was matched against the institutional anesthesiology database to identify the patients who underwent orthopedic surgery during that same hospital admission. Finally, patients who underwent multiple extracranial surgeries or surgery beyond 2 weeks of TBI were excluded to compile the final list of eligible patients.

Trauma registry records were used to abstract demographics and select clinical characteristics, including injury severity scores, and outcomes including discharge disposition, discharge GCS, and mortality. Anesthetic and intraoperative physiological data was obtained from the electronic anesthesia records and immediate postoperative physiological data and intervention information from the intensive care unit records. The intraoperative physiological data were electronically captured every minute. However, the output of this data could be abstracted only for every 5-minute period. Official reports of head CT scans signed by attending radiologists, which were documented in the medical records were used to abstract radiographic diagnoses pertaining to TBI.

Institutional Anesthetic Management of TBI

During the study period, there was no standardized protocol for timing of orthopedic surgery in patients with TBI. All patients were cleared for surgery by a neurosurgeon based on stable neurological condition, CT scans, and ICP while considering the urgency of orthopedic procedure. There was also no formal protocol for anesthetic care. However, consistent with best evidence, patients typically received general anesthesia with <1.0 minimum alveolar concentration isoflurane/sevoflurane without nitrous oxide, or intravenous anesthesia with propofol infusion and intermittent boluses of rocuronium/vecuronium and opioid at the discretion of the attending anesthesiologist. Arterial catheters were used for continuous blood pressure monitoring in all patients and blood was sampled for $PaCO_2$, and glucose at the discretion of the anesthesia team. ICP monitoring was continued intraoperatively in patients who had ICP monitors in situ. Mannitol (0.5 to 1 g/kg) and/or hyperventilation were used to treat intracranial hypertension, if required. Isotonic non–glucose-containing intravenous fluids were used intraoperatively, and colloid use was infrequent. Transfusion of blood products and treatment of hypotension including the choice of vasopressor agents was at the discretion of the attending anesthesiologist. Normothermia was targeted by adjusting the temperature of forced air blankets and intravenous fluids. All patients received head CT scans immediately postoperatively.

Definitions

Secondary insults were defined as: Systemic hypotension: systolic blood pressure <90 mm Hg[18]; Cerebral hypotension (low CPP): CPP <50 mm Hg[17]; Intracranial hypertension: ICP >20 mm Hg[19]; Hypercarbia: end-tidal $CO_2 > 40$ mm Hg; Hypocarbia: end-tidal $CO_2 < 30$ mm Hg in the absence of intracranial hypertension; Hyperglycemia: blood glucose >200 mg/dL; Hypoglycemia: blood glucose <60 mg/dL; Hyperthermia: core temperature $>38^{\circ}$C.

We used end-tidal CO_2 rather than $PaCO_2$ values to define hypercarbia and hypocarbia due to lack of sampling of arterial gases in majority of patients. Although the definition of hyperglycemia is frequently debated, we used a threshold of blood glucose >200 mg/dL because in clinical practice, values above this usually trigger treatment.

Patient level outcomes were defined as:

- Worse postoperative CT scan: new/increased cerebral edema, hemorrhage, mass effect, midline shift or hypodensity within 24 hours of surgery.
- Postoperative intracranial hypertension: ICP >20 mm Hg within 24 hours of surgery requiring treatment.
- Postoperative decrease in GCS score: best GCS score within 24 hours of surgery lower than preoperative GCS score by ≥ 2 points.
- Immediate postoperative escalation of care: new onset institution of ICP monitoring or new treatment of intracranial hypertension/cerebral hypotension (low CPP) or unexpected mechanical ventilation or use of vasopressors.

Statistical Analysis

The analysis was performed using SPSS version 19 (SPSS Chicago, IL). Descriptive statistics were used to describe preoperative clinical characteristics, CT scan lesions, timing of craniotomy or orthopedic surgery after TBI, intraoperative characteristic, and secondary insults. Data are reported as number (percent), median (range), and mean (SD) as appropriate. Categorical data (use of inhalation anesthesia, presence or absence of intraoperative secondary insults—systemic hypotension, intracranial hypertension, cerebral hypotension, hypercarbia, hypocarbia, hyperthermia, hyperglycemia) for patients undergoing surgery within 2 days after TBI versus 3 to 14 days after TBI were compared using either Pearson χ^2 or Fisher exact test. Independent-samples median test was used for continuous variables (age, anesthesia and surgical time, total crystalloid, estimate blood loss, blood pressure, ICP, CPP, end-tidal CO_2, temperature, and blood glucose). Univariate analysis was used to test the association of intraoperative secondary insults and timing of orthopedic surgery with immediate postoperative neurological outcomes (worse head CT scan, intracranial hypertension, and escalation of care). Bonferroni correction was used to account for multiple comparisons. Statistical significance was considered for values of $P < 0.05$.

RESULTS

During the study period 3990 patients were admitted to Harborview Medical Center with TBI and polytrauma, and 480 (12%) of these patients underwent extracranial surgery. In total, 78 patients met all inclusion criteria for this study and were included in the final analysis.

Preoperative Characteristics

The preoperative characteristics are detailed in Table 1. Briefly, the median age of eligible patients was 41 (18 to 81) years and 53 (68%) of them were males. The median admission GCS was 3 (3 to 11) and the median preoperative GCS was 10 (3 to 15). Forty-one (52%) patients had surgery within 2 days of TBI. There was no difference in the age or sex of patients who had surgery within 2 days or between 3 and 14 days after TBI (median age, 34 [18 to 86] vs. 47 [18 to 83] y; $P = 0.11$and 75% vs. 59% males; $P = 0.13$). Patients who underwent surgery 3 to 14 days after TBI had higher ISS score (47 [27 to 59] vs. 34 [9 to 66], $P < 0.001$), higher AIS score (5 [2 to 5] vs. 4 [2 to 5], $P < 0.001$) and lower preoperative hematocrit (27% [18% to 45%] vs. 33% [22% to 41%], $P = 0.007$) compared with the patients who had undergone surgery within 2 days.

TABLE 1. Preoperative Characteristics of Patients With Traumatic Brain Injury (TBI) Who Underwent Single Orthopedic Surgery Within 14 Days of Moderate-Severe TBI (n = 78)

Preoperative Characteristics	
Age (y)	41 (18-81)
Male sex	53 (68)
Admission Head Abbreviated Injury Scale	4 (2-5)
Admission Injury Severity Score	35 (14-59)
Admission Glasgow Coma Scale (GCS) score	3 (3-11)
Traumatic brain injury type	
Subarachnoid hemorrhage	53 (68)
Subdural hemorrhage	14 (18)
Contusion/concussion	8 (10)
Other TBI	3 (3.8)
Preoperative GCS score	10 (3-15)
Preoperative systolic blood pressure (mm Hg)	120 (88-192)
Preoperative intracranial pressure (mm Hg) (n = 20)	11 (1-22)
Preoperative cerebral perfusion pressure (mm Hg) (n = 20)	77 (49-118)
Preoperative hematocrit (%)	30 (21-39)
Intubated and mechanically ventilated before surgery	53 (68)
Craniotomy within the same 14 d	3 (4.2)
Timing of surgery orthopedic surgery after TBI (d)	
0-2	41 (52)
3-14	37 (48)

Data are presented as number (%) or median (range).

Intraoperative Characteristics

Seventy-four (94.8%) patients received inhalational anesthesia. There was no difference in the duration of anesthesia and surgery, choice of inhalational anesthesia, and total doses of narcotics between the patients who underwent early versus delayed surgery (Table 2). Patients in both groups were comparable in terms of intraoperative fluid volume administered, estimated blood loss, number of episodes of hypotension, and intraoperative blood transfusion (Table 2).

Intraoperative Secondary Insults

Eighty-seven percent of the patients had at least 1 intraoperative secondary insult and 50% had 2 or more secondary insults (Table 3). The most common intraoperative secondary insult was systemic hypotension, followed by intracranial hypertension and cerebral hypotension. Preoperative pneumonia was associated with intraoperative hypercarbia (0.04). There was no difference in intraoperative secondary insults based on the timing of orthopedic surgery except that hyperthermia was more common in patients who had surgery 3 to 14 days after injury compared with those who had surgery within 2 days. However, none of these patients had new onset intraoperative hyperthermia and 19% and 21% patients in the 2 groups, respectively, had preoperative hyperthermia ($P = 0.55$). Serum sodium levels were documented for preoperative, intraoperative, and postoperative for 48 patients. The median preoperative, intraoperative, and postoperative sodium values for these patients were 140 (132 to 157) mmol/L, 139 (135 to 154) mmol/L, and 140 (131 to 150) mmol/L, respectively ($P = 0.96$).

Association Between Intraoperative Secondary Insults and Timing of Surgery on Immediate Postoperative Neurological Outcomes

Of the 78 patients, worsening of postoperative head CT scan occurred in 6 (7%) patients and postoperative

TABLE 2. Intraoperative Characteristics Based on Timing of Orthopedic Surgery After Moderate-Severe TBI

	Total (n = 78)	Orthopedic Surgery Within 2 d of TBI (n = 41)	Orthopedic Surgery 3-14 d After TBI (n = 37)	*P* (95% CI)
Anesthesia time (min)	196 (44-456)	199 (63-420)	192 (40-456)	0.36 (−28.26, 55.67)
Surgical time (min)	136 (0-378)	142 (27-378)	126 (0-338)	0.07 (−22.25, 60.09)
Total crystalloid (mL)	1553 (100-4500)	1850 (350-4500)	1500 (100-3800)	0.9 (−48.39, 884.23)
Estimated blood loss (mL)	100 (0-1000)	100 (0-1000)	75 (0-850)	0.3 (−83.71, 111.24)
Patients requiring blood transfusion	9 (15.3)	3 (3.8)	6 (7.6)	0.21 (−146.34, 49.46)
Inhalation anesthesia	74 (94.8)	38 (92)	36 (97)	0.6 (0.54, 14.92)
Fentanyl (mcg)	250 (0-750)	250 (0-600)	250 (0-750)	0.1 (−103.90, 36.40)
Hydromorphone (mg)	2 (0-7)	2 (0-7)	1.2 (0-6)	0.2 (−0.30, 1.62)
Phenylephrine (mcg)	300 (0-1824)	200 (0-1337)	400 (0-1824)	0.4 (−6.23, 2.05)
Episodes of hypotension	1 (0-26)	3 (0-26)	2 (0-17)	0.7 (−2.50, 3.52)

Data are presented as number (%) or median (range).
CI indicates confidence interval; TBI, traumatic brain injury.

intracranial hypertension in 7 (8%) patients, whereas 9 patients (11.5%) required escalation of care and 9 (11.5%) patients had a postoperative decrease of GCS score by ≥ 2 (Table 4). Intraoperative secondary insults that were associated with worsening of postoperative head CT scan were cerebral hypotension ($P = 0.03$) and hypocarbia ($P = 0.04$). Also, intraoperative cerebral hypotension was associated with postoperative decrease of GCS score by ≥ 2 ($P = 0.01$). Postoperative escalation of care was associated with intraoperative intracranial hypertension ($P = 0.03$) and cerebral hypotension ($P < 0.001$). The most common indication of postoperative escalation of care was intracranial hypertension which itself, was not associated with any specific intraoperative secondary insult. After Bonferroni correction for multiple comparisons, only the association between cerebral hypotension and postoperative escalation of care remained significant ($P < 0.001$). There was no association between timing of surgery and postoperative worsening of head CT scan ($P = 0.73$), intracranial hypertension ($P = 0.18$), or escalation of care ($P = 0.22$).

Postoperative GCS for the entire cohort was 9.5 (3 to 15) and was not significantly different from the preoperative GCS ($P = 0.93$). Overall in-hospital mortality in this cohort was 2.5% and 17 (22%) patients had discharge GCS < 13. There was no association between intraoperative secondary insults and discharge GCS < 13 or in-hospital mortality. The low mortality in this cohort likely represents a selection bias because these patients probably underwent surgery as they were expected to survive. The patients with TBI and polytrauma who were unlikely to survive and had higher mortality rate, probably died before undergoing orthopedic surgery and were therefore not included in this cohort.

Fifteen (19%) patients in this cohort had pneumonia, 2 (2.5%) had pleural effusion. None of the patients had Adult Respiratory Distress Syndrome but 2 patients suffered postoperative pulmonary embolism. One patient had sepsis.

TABLE 3. Intraoperative Secondary Insult Data for Orthopedic Surgery in Patients With Moderate-Severe TBI (n = 78)

	Overall (N = 78)	Orthopedic Surgery Within 2 d of TBI (n = 41)	Orthopedic Surgery 3-14 d After TBI (n = 37)	*P* (95% CI)
Systemic hypotension (SBP < 90 mm Hg)	47 (60)	25 (61)	22 (59)	0.89 (0.38, 2.33)
Lowest SBP (mm Hg)	50 (0-88)	87 (65-88)	78 (0-88)	0.66 (−6.77, 7.13)
Intracranial hypertension (ICP > 20 mm Hg)	10/20 (50)	5/8 (62)	5/12 (42)	0.60 (0.24, 3.35)
Highest ICP (mm Hg)	19 (10-44)	21 (14-44)	19 (10-38)	0.65 (−6.37, 10.62)
Cerebral hypotension (CPP < 50 mm Hg)	9/20 (45)	4/8 (50)	5/12 (42)	0.55 (0.17, 2.80)
Lowest CPP (mm Hg)	56 (29-101)	51 (29-83)	58 (40-101)	0.65 (−22.79, 12.62)
Hypercarbia ($ETCO_2$ > 40 mm Hg)	25 (32)	13 (32)	12 (32)	0.98 (0.50, 2.95)
Highest $ETCO_2$ (mm Hg)	51 (30-68)	42 (30-68)	42 (30-60)	0.50 (−4.38, 4.45)
Hypocarbia ($ETCO_2$ < 30 (mm Hg)	33 (29)	11 (27)	12 (32)	0.23 (0.50, 3.47)
Lowest $ETCO_2$ (mm Hg)	31 (20-51)	31 (20-41)	31 (23-51)	0.72 (−3.54, 0.87)
Hyperthermia (core temperature > 38°C)	9 (12)	3 (7.5)	6 (16)	**0.02 (0.09, 1.17)**
Highest temperature (°C)	37.3 (35.6-39.1)	37.3 (36.5-38.3)	37.4 (35.6-39.1)	0.09 (−0.64, 0.11)
Hyperglycemia (blood glucose > 200 mg/dL)	2/30 (6.7)	1/13 (7.7)	1/17 (5.9)	0.47 (0.05, 14.92)
Highest blood glucose (mg/dL)	129 (83-293)	148 (87-293)	122 (83-240)	0.14 (−23.00, 46.56)

Data are presented as number (%) or median (range).
P value < 0.05 are statistically significant.
CPP indicates cerebral perfusion pressure; $ETCO_2$, end-tidal CO_2; ICP, intracranial pressure; SBP, systolic blood pressure; TBI, traumatic brain injury.

TABLE 4. Univariate Analysis for Association of Intraoperative Secondary Insults and Timing of Orthopedic Surgery With Immediate Postoperative Neurological Outcomes in Patients With Moderate-Severe Traumatic Brain Injury (n = 78)

Intraoperative Secondary Insult	Worse Postoperative Head CT scan (n = 6)*	Postoperative Intracranial Hypertension (n = 7)†	Postoperative Escalation of Care (n = 9)‡	Postoperative GCS Decrease ≥ 2 (n = 9)	Discharge GCS < 13 (n = 15)
Systemic hypotension (SBP < 90 mm Hg) (n = 47)	0.16	0.53	0.76	0.25	0.08
Intracranial hypertension (ICP > 20 mm Hg) (n = 10)	0.26	0.24	**0.03**	0.67	0.26
Cerebral hypotension (CPP < 50 mm Hg) (n = 9)	**0.03**	0.05	**< 0.001**	**0.01**	0.79
Hypercarbia (end-tidal CO_2 > 40 mm Hg) (n = 25)	0.40	0.15	0.87	0.57	0.82
Hypocarbia (end-tidal CO_2 < 30 mm Hg) (n = 33)	**0.04**	0.18	0.30	0.79	0.72
Hyperglycemia (blood glucose > 200 mg/dL) (n = 2)	0.90	0.89	0.12	0.17	0.29
Hyperthermia (core temperature > 38°C) (n = 9)	0.40	0.38	0.70	0.33	0.81

Data presented as *P*-values for the relationship.

After Bonferroni correction for multiple comparisons, only association between cerebral hypotension and postoperative escalation of care remained significant ($P < 0.001$).

*Worse postoperative head computed tomographic scan: New/increased cerebral edema, hemorrhage, mass effect, midline shift, or hypodensity within 24 hours of surgery.

†Postoperative intracranial hypertension: intracranial pressure > 20 mm Hg within 24 hours of surgery requiring treatment.

‡Postoperative escalation of care: new institution of ICP monitoring/treatment of intracranial hypertension/cerebral hypoperfusion or unexpected mechanical ventilation/use of vasopressors within 24 hours of surgery.

P value < 0.05 are statistically significant.

CPP indicates cerebral perfusion pressure; GCS, Glasgow Coma Scale; ICP, intracranial pressure; SBP, systolic blood pressure.

DISCUSSION

Our results indicate that in adult patients undergoing orthopedic surgery within 2 weeks of moderate-severe TBI (1) intraoperative secondary insults were common; (2) the most common intraoperative secondary insult was systemic hypotension followed by intracranial hypertension, cerebral hypotension, hypercarbia, and hypocarbia; and (3) intraoperative cerebral hypotension was associated with postoperative escalation of care. These findings provide an estimate of the burden of intraoperative secondary insults for TBI patients requiring orthopedic surgery and their association with immediate postoperative outcomes. Secondary insults can occur during any phase of TBI from prehospital to the intensive care but the intraoperative period is physiologically distinct. Although TBI itself can lead to myocardial and pulmonary dysfunction,[20,21] the anesthetic agents also affect cerebral[22–24] and cardiovascular physiology.[25,26] In addition, surgical intervention leads to fluid shifts and blood loss. Secondary insults during craniotomy for TBI have been reported,[9,10,27–32] and as evidenced by our data here, secondary insults are also common during orthopedic surgery in patients with TBI and may contribute to worse outcomes. Therefore, anesthesiologists can potentially contribute to improving TBI outcomes by reducing the burden of secondary insults during craniotomy as well as extracranial surgery.

Systemic Hypotension and Intracranial Hypertension During Orthopedic Surgery in TBI

The higher prevalence of intraoperative systemic hypotension we observed in this series (60%) compared with the 7% to 43% reported by previous studies[11–14] is likely due to more accurate capturing of physiological data with the electronic medical record system. All patients in our series had continuous arterial blood pressure recording but it is unclear if the previous studies used invasive or noninvasive blood pressure measurements. Nevertheless, it is concerning that majority of patients were hypotensive under anesthesia irrespective of the timing of surgery. Unlike Townsend et al[11] who recommended delaying surgery to prevent secondary insults including hypotension, similar to our results, Velmahos et al[12] and Kalb et al[14] reported no difference in intraoperative hypotension based on timing of orthopedic surgery. Interestingly, the prevalence of intraoperative hypotension in this series is similar to the 65% prevalence we recently reported during craniotomy for TBI[9] indicating that hypotension is a common problem, irrespective of the type of surgery in TBI patients. Avoidance of hypotension may be crucial even in patients undergoing surgery days after TBI because cerebral autoregulation may be impaired up to 2 weeks after moderate-severe TBI,[33] predisposing them to the risk of cerebral ischemia. Although we did not observe an association of intraoperative hypotension with postoperative head CT changes, intracranial hypertension or escalation of care, we cannot rule out cerebral ischemia due to hypotension because cerebral oxygenation and cerebral blood flow were not monitored during surgery nor can we rule out subtle brain damage or impact on long-term neurological outcomes. Strategies for avoiding/rapidly treating systemic hypotensionduring extracranial surgery include adequate fluid/blood product replacement, avoiding anesthetic/narcotic overdose, and rational use of inotropes/vasopressors.

Approximately half of the 20 patients in our series who had ICP monitoring, had intracranial hypertension and cerebral hypotension during general anesthesia. However, these estimates may be conservative as the majority of our patients did not have ICP monitoring. Increased ICP intraoperatively may be due to cerebral

vasodilatory property of inhaled anesthetic agents,[34] inadvertent hypercarbia,[35] and improper positioning.[36] Although majority of the patients in our series received volatile anesthetics, the anesthetic concentration was below 1.0 minimum alveolar concentration and hence, unlikely to contribute to ICP elevations.[37,38] Using CPP < 70 mm Hg to define low CPP based on the existing guidelines at that stage, Townsend et al[11] and Kalb et al[14] reported 74% and 26% patients as having intraoperative cerebral hypotension. Using the current Brain Trauma Foundation guidelines definition, we observed that 45% patients had intraoperative CPP < 50 mm Hg with no difference based on the timing of surgery. Avoidance of intracranial hypertension and maintenance of cerebral perfusion, 2 major goals of TBI management, seem to be relatively unmet intraoperatively.

Hypercarbia, Hypocarbia, and Hyperglycemia During Orthopedic Surgery in TBI

Our observation of the high prevalence of inadvertent hypercarbia as well as hypocarbia calls for closer attention to intraoperative ventilatory management. Although hypercarbia can lead to intracranial hypertension,[39] hypocarbia can cause cerebral vasoconstriction contributing to cerebral ischemia.[40] In the absence of intracranial hypertension, normocapnea is recommended in TBI patients, especially in the absence of monitoring of cerebral blood flow or cerebral oxygenation.[15] Although hypercarbia and hypocarbia may be more accurately defined by $PaCO_2$ values, we used end-tidal CO_2 values because $PaCO_2$ was documented in only 27 patients. Interestingly, none of the previous studies examined inadvertently high or low CO_2 values and our study provides the first estimates of these secondary insults during extracranial surgery in TBI. Intraoperative hyperglycemia was uncommon in this series although glucose was monitored in less than half the patients during surgery.

Hyperthermia During Orthopedic Surgery in TBI

Hyperthermia is detrimental to the injured brain because it is associated with increased ICP and higher mortality.[41] Perioperative hyperthermia may be due to infection, noninfectious inflammation, allergic reactions, and blood in the fourth ventricle but intraoperative hyperthermia is rare, possibly due to the redistribution of body heat from the core to periphery and the impairment of thermoregulation by anesthetic agents.[42] In fact, there may be a dose-dependent inhibition of fever with volatile anesthetics and opioids.[42] In this cohort, hyperthermia was present preoperatively in 19% and 21% patients who underwent surgery 3 to 14 days and <2 days after TBI. Under anesthesia, hyperthermia was still present in 16% and 7.5%, respectively, but no patient had new onset hyperthermia. The significant difference in intraoperative hyperthermia between the patients undergoing surgery at different time periods may represent closer attention to temperature management under anesthesia in 1 group. Irrespective, our data suggest a need for closer monitoring of temperature under anesthesia.

Impact of Intraoperative Secondary Insults on Neurological Outcomes in TBI

Intraoperative secondary insults during craniotomy for TBI has been shown to be associated with increased risk of poor outcome.[27,29,30,43] Townsend et al[11] observed that patients with intraoperative ICP > 20 mm Hg or CPP < 70 mm Hg during femur fixation had a low chance of good neurological outcome after TBI. In univariate analysis, we found an association of ICP > 20 mm Hg, CPP < 50 mm Hg, and hypocarbia with immediate postoperative radiologic worsening of TBI and escalation of the level of care, irrespective of the timing of surgery. Intraoperative CPP < 50 mm Hg was also associated with postoperative decrease of GCS score by ≥2 points. However, intraoperative secondary insults were not associated with mortality, discharge GCS <13 or discharge disposition probably due to rapid correction of secondary insults under anesthesia and due to postoperative escalation of care incorporating appropriate interventions although this could also be due to relatively low mortality overall and small sample size. Moreover, after Bonferroni correction for multiple comparisons, only association between cerebral hypotension and postoperative escalation of care remained significant ($P < 0.001$).

Limitations

The limitations of this study include the retrospective study design and the reliance on medical records not designed for data collection specific to this study. The possibility of artifacts making into the electronic anesthesia records cannot be completely excluded. Also, there is no reliable method to eliminate these artifacts. Moreover, we did not analyze the impact of duration of each secondary insult on outcomes. It is possible that brief periods of secondary insults may cause less injury to the brain. Very few patients received intravenous anesthesia limiting our ability to compare anesthetic agents and few patients had ICP monitoring that may affect our estimates of intraoperative intracranial hypertension and cerebral hypotension. We cannot rule out more subtle neurological damage resulting from secondary insults and we do not have long-term outcome data. Although there seems no association between radiologic worsening and relatively coarse indices of outcome at this stage, there's the possibility that a more detailed functional assessment may reveal an association, which would require a prospective trial. We did not have the Therapeutic Intensity Level scores. Instead, we used "escalation of care" as a measure of increase in the postoperative treatment intensity. However, it is difficult to ascertain whether the escalation of care was due to neurological worsening or altered physiological need as a result of exposure to anesthetic agents, narcotics, or neuromuscular blocking agents. Although the exact etiology of escalation in care may not be clear, in general, it would reflect a worse physiological status after exposure to anesthesia/surgery. Another limitation is the

rather small number of patients to examine the impact of timing of surgery on outcomes. We performed Bonferroni correction to account for the multiple univariate associations. However, the Bonferroni correction is highly conservative and may fail to detect the differences. Larger studies would be needed to further confirm the association of intraoperative secondary insults with postoperative outcomes. Our results also need to be interpreted in light of the fact that the patients had recovered to variable degrees by the time of extracranial surgery and we cannot ascertain whether the secondary insults were better (or worse) tolerated by patients who have recovered to be extubated after TBI (compared with those who continued to remain intubated and required ICP monitoring). Despite the above limitations, this study highlights an important and under studied aspect of anesthetic care, which is typically not represented in studies of TBI.

In summary, despite the advancements in anesthetic care, intraoperative secondary insults were common during orthopedic surgery in patients with TBI and were associated with postoperative escalation of care. Strategies to minimize intraoperative secondary insults may potentially improve TBI outcomes.

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